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IN-SITU BUFFERED FORMULATION: AN EFFECTIVE APPROACH FOR ACID LABILE DRUG

Preeti Khulbe *, Birendra Shrivastava, Pankaj Sharma and Ajay Kumar Tiwari

Jaipur National University, Jagatpura Jaipur, Rajasthan, India.

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Correspondence to Author:
Preeti Khulbe

90/66 sector 9 Pratap Nagar, Sanganer Jaipur, Rajasthan, 302033, India.

E-mail: khulbe.preeti@yahoo.in

ABSTRACT: "Acid labile drug" means a drug that is easily destroyed in acidic environment, Stomach is the main site for drug absorption mainly by oral rout. The pH of the stomach is acidic so the absorption of acid labile drugs through stomach is difficult. For this resign the drugs should be formulated as enteric coated or may be administered through parenteral rout. These approaches are effective but they increase the cost of the dosage form. So for making the acid labile drug effective in acidic environment one of the best approach is *in-situ* buffer formulation. These are the formulation containg agents which immediately buffer the internal environment of the body and increases the stability of acid labile drugs inside the body. This article covers the possible approaches for buffer formulation, formulations could be possible, method of preparation and evaluation of *in-situ* buffer formulation. The articles the examples of agents can be used as buffers.

INTRODUCTION: "Acid labile drug" means a drug that is easily destroyed in acidic environment. Stomach is the main site for drug absorption mainly by oral rout. The pH of the stomach is acidic so the absorption of acid labile drugs through stomach is difficult.[1]

The most commonly used acid labile drugs are amylase, aureomycin, bacitracin, beta carotene, cephalosporins, Chloromycetin, cimetidine, cisapride, cladribine, clorazepate, deramciclane, didanosine, digitalis glycosides, dihydrostreptomycin, erythromycin, etoposide, famotidine, hormones (in particular estrogens, insulin, adrenalin and heparin), lipase, milameline, novobiocin, pancreatin, penicillin salts, polymyxin, pravastatin, progabide, protease, quinapril, ranitidine, streptomycin, subtilin, sulphanilamide or acid-labile proton pump inhibitors like esomeprazole, lansoprazole, minoprazole, omeprazole, pantoprazole or rabeprazole. Amylase, lipase, protease [2, 3].

Proton pump inhibitors are most commonly used drug which are unstable in acidic environment i.e. acid labile. Proton pump inhibitors are used to supress the acid of the stomach. The use of Proton pump inhibitors is not limited it is also used for the suppression of ulcer related to stress and nonsteroidal anti-inflammatory drugs (NSAIDs). Long term use NSAIDs causes serious ulcer [4].

Approaches to increase acid stability of acid labile drugs: Acid labile drugs tend to be unstable at acidic pH and therefore there are some approaches which are generally used to overcome this problem. As per the literature there are three major approaches which can be used to enhance acid stability of the drug.

Enteric coating of the drug: Enteric coating: If a tablet is described as having an 'enteric coating' or 'gastro-resistant', it means that there is a coating which holds the tablet together when in the stomach.

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The fact is that the stomach is acidic and the intestines, where food goes after the stomach is basic. The coating is so formed that in acid conditions the coating is intact whereas it can break down in non-acid conditions and therefore release the drug in the intestines. The drugs which most commonly cause stomach ulcers like aspirin, diclofenac and naproxen are frequently available with enteric coatings. Other than that proton pump inhibitors, the drugs which stops the stomach from producing acid, are itself broken down in acid and therefore the drug generally has an enteric coating around it either as a granule in the capsules or as a granule in the dispersible form**.** Other than that there are many drugs which are acid labile can be used in enteric coated [5, 6, 7].

Parenteral dosage form: Parenteral dosage form are the formulations which are directly releases into the systemic circulation. These are in the form of injections. Because this is an injectable dosage form and it breaks the protective barrier of the skin, the product must be free of contamination. This would require some form of control over how these products are produced. Because these formulations directly inserted to the site of action so by changing the site of delivery through parenteral dosage form the stability can be enhanced [8].

Buffer formulation: these are the dosages forms which are used to increase the acid stability of the drug by increasing the pH of the site of release. These formulations may increase the pH of the delivery site and then release the drug so that it does not appear in acidic environment [9].

From all the approaches available, the most common approach is enteric-coated dosage forms to prevent acid degradation. However, these drugs are stable at alkaline pH, and gets destroyed as the pH goes to lower side i.e. gastric environment. In spite of advantages there are many disadvantages of enteric coating as well:

- Disruption of enteric coating by chewing
- Late onset of action by these type of formulation.
- Onset may vary with gastric emptying.

The disruption of enteric coating by any reason may degrade the drug by gastric acid. When enteric coating reaches to stomach it will first go to intestine then after reaching the intestine the coating will dissolve then the drug will available for absorption. So by enteric coating formulation the late onset of action always seen. The other fact is that if the gastric empting is delay the drug absorption is delay and wise versa. So the onset of action of drug will depends on gastric empting. Sometime due to poor processing conditions cracks may appear in the coating which allow the gastric fluid to penetrate the coating which will leads to drug degradation [10].

Introduction to buffer: The term buffer means any compound or combination that increase the pH of the system in which they dispersed or dissolved. There are two buffers 1) water insoluble buffer 2) water soluble buffers. Water insoluble buffer means the solubility in water is 1 gm in 1000ml. The another type of buffer is water soluble buffer, which can be defined as the buffer having solubility 1 gm per 100 ml [11].

Buffers are aqueous solutions containing partly neutralized weak acids or bases that show little change in pH (H+ concentration) whatever ions are added. Requirements should be considered for the choice of the buffer, and it's use in each application. I.e. the pH should be determined at the final temperature, in presence of salts (i.e. phosphate pH change with salts concentration) near the pKa of the buffering compound. The buffering compound should not absorb at wavelengths (i.e. at 240-270nm for mass spectrometry). Classic used buffering agents are mineral buffers (Phosphate, Borate, Citrate, Glycine), but also several organic buffers (Glycine, DEA). Many requirements should be met (buffering range, solubility, compatibility with spectrometric or immunométric or cell assays) and several other points considered such as habits, availability and price.

As a result, standard buffer, and even any choosen buffer are often not ideal at one point or the other, and one might take benefits from more specific and new buffers. Biological buffers differ from classic mineral ones to several points: they have pKa values closer to physiological pH (between 6 and 8). These buffers are not toxic to cells, and are not absorbed through cell membranes.

The concentration, temperature, and ionic composition of the medium has minimal effect on the buffering capacity [12].

Buffers are necessary to maintain both solubility of the active ingredient and stability of the product. Chelating agents are added to complex and thereby inactivate metals, including copper, iron, and zinc, which generally catalyze oxidative degradation of drugs. Inert gases are used to displace the air in solutions and enhance product integrity of oxygen-sensitive drugs [13].

Buffering agents can be necessary to maintain pH of the formulation to [14]:

- Ensure physiological compatibility
- Maintaining/optimising chemical stability
- Maintaining/optimisinganti-microbial effectiveness
- Optimise solubility (or insolubility if taste is an issue)

***In situ* buffered formulation:** For the prevention of acid labile drug from degradation or making the immediate release formulation of acid labile drug buffer can be used. So for this in situ buffer is an effective approach. It creates the macro environment in the stomach by buffer. Two approaches may be used either the micro environment and the macro-environment. In macro-environment whole stomach will buffer by buffering agents [15].

Advantage of *in situ* buffered formulation [16]:

1. Maintenance of pH
2. Enhancement of stability
3. Decrease in gastric irritation
4. Increase in onset of action
5. Patient compliance

Types of buffers: Buffers can mainly classified as : water soluble and water insoluble buffers.the examples of water insolulbe buffer are, aluminum hydroxide, dihydroxy aluminum sodium carbonate, calcium carbonate, aluminum phosphate, aluminum carbonate, magnesium hydroxide dihydroxy aluminum amino acetate, magnesium oxide, magnesium trisilicate, aluminum phosphate, magnesium carbonate and their combinations. The examples of water soluble buffer includes, tripotassium phosphate, meglumine, sodium carbonate, sodium citrate, calcium gluconate, disodium hydrogen phosphate, sodium bicarbonate dipotassium hydrogen phosphate, sodium tartarate, sodium acetate, calcium glycerophosphate, tromethamine, magnesium oxide and their combinations [17, 18].

***In situ* buffer formulations could be possible:**

Buffer tablets: Tablets may be defined as the solid unit dosage form of medicament or medicaments with or without suitable diluents and prepared either by molding or by compression. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. Tablets are simple and convenient to use. They provide an accurately measured dosage of the active ingredient in a convenient portable package, and can be designed to protect unstable medications or disguise unpalatable ingredients. Coloured coatings, embossed markings and printing can be used to aid tablet recognition. Manufacturing processes and techniques can provide tablets special properties, for example, sustained release or fast dissolving formulations. Buffer tablet may be prepared by selecting different types of buffering agents then compressed by the suitable compression machine. Buffer tablets may be used as the in situ buffering, whatever the pH required. Examples of buffer tablets are: Buffer hydroin, Loba chemie pH buffer tablet, Gurr Buffer Tablets. Gurr buffer tablets offer a convenient way to prepare a pH 6.8 phosphate buffer for dilution of Giemsa stain used in G-banding of chromosomes for cytogenetic analysis. Simply add one buffer tablet to one liter of distilled water and stir until dissolved [19, 20].

Buffer capsules: Capsule is the most versatile of all dosage forms. Capsules are solid dosage forms in which one or more medicinal and inert ingredients are enclosed in a small shell or container usually made of gelatin. There are two types of capsules, “hard” and “soft”. The hard capsule is also called “two piece” as it consists of two pieces in the form of small cylinders closed at one end, the shorter piece is called the “cap” which fits over the open end of the longer piece, called the “body”. The soft gelatin capsule is also called as “one piece”. In case of buffered capsule hard gelatin capsule is mainly used.

For making in situ buffer capsule selected buffering agents are usually placed in a capsule, this capsule when dissolve inside provides the buffering environment. Examples of buffering capsules are tri-chek buffer capsule; Carbonate-Bicarbonate Buffer capsule; Phosphate-Citrate Buffer with Sodium Perborate capsule [21].

Buffer Microspheres: Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature and ideally having a particle size less than 200µm. By using buffer microspheres, it is easy to control or continue the release of buffering agent up to prolonged period. This is the important approach in delivering therapeutic substance to the target site in sustained and controlled release fashion. They facilitate accurate delivery of small quantities of potent drug and reduced concentration of drug at site other than the target organ or tissue. They provide protection for unstable drug before and after administration, prior to their availability at the site of action. They provide the ability to manipulate the in vivo action of the drug, pharmacokinetic profile, tissue distribution and cellular interaction of the drug. They enable controlled release of drug. Examples: Narcotic, Antagonist, Steroid hormones.

In case of making buffered formulation microspheres is a good option. For this different microspheres can be prepared by specified methods. In this buffering agents or ingredients may incorporate into the formulation in any of the phase. So that when the buffering agent releases it causes increase in pH inside the body. Mixture of microspheres in a single formulation (microspheres filled in capsules) also can be used in case of incompatibility with drugs [22].

Method of preparation *in situ* buffer formulation:

Buffer tablet:

1. Direct compression: Processing steps are:
Raw material → Weighing → Screening → Mixing → Compression: Direct compression consists of compressing tablets directly from powdered materials without modifying physical nature of materials. This method is applicable for crystalline chemicals having good compressible characteristic and flow properties. So the buffering agents having such quality may be formulated as buffer tablet by direct compression.

Advantages:

1. Low labour input
2. A dry process
3. Fewest processing steps

Disadvantages: During handling of dry materials static charge may form which may present uniform distribution.

2. Dry granulation: Processing steps are:
Raw material → weighing → Screen → Mixing → Slugging → Milling → Screening → Mixing → Compression: When tablet ingredients are sensitive to moisture and/or unable to withstand elevated temperature during drying and when the tablet ingredient have insufficient cohesive properties, slugging may be used to form granules. This method is referred to as dry granulation. This technique is used in case of moisture sensitive buffering agents. In case of buffer tablet, it is a rarely used technique.

Compression granulation involves the compaction of the components of a tablet formulation by means of flat punch. These compact masses are called slug and the process is called slugging. Slugs are then milled and screened to produce a granular form. On large scale operation compression granulation can be performed on specially designed machine called Roller compactor.

3. Wet granulation: Processing steps are: Raw materials → Weighing → Screening → Wet massing → Sieving/Milling → Drying → Screening → Mixing → Compression: The most widely used and most general method of tablet preparation is the wet granulation method. The buffering agents are mixed or blended well. For large-scale production twin shell blender, double cone blender, planetary mixer, sigma blade mixer, ribbon mixer etc. are commonly used. Solutions of the binding agent are added to the mixed powder with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow. If the granulation is over wetted the granules will be hard, if not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication.

The wet mass is forced through a 6 or 8 mesh (Mesh no. is the number of wires passing through an inch) screen or several mills can be used. Moist materials from wet milling steps is placed on large trays and placed in drying chambers with a circulating air current and thermostable heat controller. Commonly used dryers are tray dryer, fluidized bed dryer. After drying, the granulation is reduced in particle size by passing smaller mesh screen [23].

Buffer capsule: Buffer capsule is generally formulated by filling buffering agents in the form of powder, granules or tablet. The method of preparation of granules and tablet is same as discussed in buffer tablet. In case of powder filling the buffering agent in the form of dry powder first weighed then sieved through a sieve shaker to remove forgin matter. Then the powder is mixed properly followed by filling of capsule. Three techniques are used for filling: Powder filling, granules filling, tablet filling [24].

Hard gelatin capsule filling machines: Hand operated and electrically operated machines are in practice for filling the capsules but for small and quick dispensing hand operated machines are quite economical. All parts of the machine are made up of stainless steel. The machines are generally supplied with additional loading trays, beds, and pin plates with various diameters of holes so as to fill the desired size of the capsules. These machines are very simple to operate, can be easily dismantled and reassembled.

Working: The empty capsules are filled into the loading tray which is then placed over the bed. By opening the handle, the bodies of the capsules are locked and caps separated in the loading tray itself which is then removed by operating the liver. The weighed amount of the drug to be filled in the capsules is placed in powder tray already kept in position over the bed. Spread the powder with the help of a powder spreader so as to fill the bodies of the capsules uniformly. Collect excess of the powder on the platform of the powder tray. Lower the pin plate and move it downward so as to press the powder in the bodies. Remove the powder tray and place the caps holding tray in position. Press the caps with the help of plate with rubber top and operate the lever to unlock the cap and body of the capsules. Remove the loading tray and collect the filled capsules in a tray. On large-scale manufacturing various types of semiautomatic and automatic machines are used. They operate on the same principle as manual filling, namely the caps are removed, powder filled in the bodies, caps replaced and filled capsules are ejected out. With automatic capsule filling machines powders or granulated products can be filled into hard gelatin capsules. With accessory equipment, pellets or tablets along with powders can be filled into the capsules.

Capsule filling devices: A number of different manually operated capsule filling devices are commercially available for filling up to 50 or 100 capsules at a time. The method of using these machines requires a careful determination of the capsule formulation. The powder is blended as previously discussed. Empty gelatin capsules are placed into the device and, oriented so that the cap is on top. The machine is worked to separate the base from the cap and the portion of the machine holding the caps is removed and set aside.

The capsule bases are allowed to “drop” into place so that the tops are flush with the working surface. The powder mix is spread over the working surface. A plastic spatula can be used carefully to spread the powder uniformly and evenly into the capsule bases or the machine can be “tapped” to spread the powder and drop it down into the capsule bases. A small device consisting of several “pegs” on a handle can be used to tamp the powder into the capsule bases gently and evenly. Any remaining powder then is spread evenly over and into the capsule bases and tamped. These procedures are repeated until all of the powder is in the capsules. The capsule caps are then fitted over the machine, fixed in place, and the filled capsules removed, dusted using a clean cloth, and packaged [25].

Buffer Microspheres:

Emulsion solvent evaporation technique: In this technique the buffering agent is dissolved in polymer which was previously dissolved in chloroform and the resulting solution is added to aqueous phase containing 0 .2 % solution of polyvinyl pyrolidone as emulsifying agent.

The above mixture was agitated at 500 rpm then the drug and polymer (eudragit) was transformed into fine droplet which solidified into rigid microspheres by solvent evaporation and then collected by filtration and washed with demineralised water and desiccated at room temperature for 24 hrs.

Emulsion cross linking method: In this method buffering agent was dissolved in aqueous gelatine solution which was previously heated for 1 hr at 40^{o}C. The solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 min at 35^{o}C, results in w/o emulsion then further stirring is done for 10 min at 15^{o}C. Thus the produced microspheres were washed respectively three times with acetone and isopropyl alcohol which then air dried and dispersed in 5mL of aqueous glutaraldehyde saturated toluene solution at room temperature for 3 hrs for cross linking and then was treated with 100mL of 10mm glyciene solution containing 0.1%w/v of tween 80 at 37^{o}C for 10 min to block unreacted glutaraldehyde [26].

Evaluation of *in situ* buffered formulation:

Evaluation of buffering capacity (Acid neutralizing capacity of buffer formulation): In this technique excess acid is provided as per the daily need of the body. The environment was selected where the formulation has to be dissolved or has to create a buffered environment. For example, if the formulation has to create buffering in stomach, excess acid is provided as per the daily need of the stomach. According to Lentner (1981) and Yamada (1999), The basal stomach fluid contains 9.6 ml of 0.1 N HCI and releases 0.5 ml of 0.1 N HCI per minute. So for making simulated gastric conditions 9.6 ml of 0.1 N HCI + 210 ml of water and titrated with excess acid (0.1 HCI) at the rate of 0.5 ml /minute for a period of 1 hour (total volume= 250 ml). For determining the acid neutralizing capacity, the prepared formulation will dissolve in the specified environment and tested for the acid neutralizing effect [1].

Evaluation of Buffered Granules:

1. Particle size & shape: Particle size of granulation affect granule flow ability, filling properties. The methods for determine particle size and size distribution are sieving, microscopy and sedimentation.

2. Surface area: release of the buffering agent depends on surface area of powder materials or granules. The most common method for determination of surface area is gas adsorption and air permeability.

3. Density: Granule density may influence compressibility, porosity, release and other properties. Generally, three types of density arise for granules:

(a) True density (l_p) = Wt/ True Volume = W/V_p

(b) Bulk density (l_b) = Wt/ Bulk Volume = W/V_b

(c) Granule density = Wt/ Granule volume = W/V_g

True Volume = Vol. excluding inter & intra granular space

Bulk Volume = Vol. including inter & intra granular space

Granule Volume = Vol. excluding inter granular space but including intra granular space.

True density can be measured by Mercury, helium displacement method and also using low surface tension liquid like benzene with the help of Pycnometer.

Bulk density can be measured by taking a known wt. of materials in a graduated measuring cylinder and tapping upto a constant reading.

Porosity directly related with true density and bulk density.

Porosity = Total empty space / Bulk volume

$= V_b - V_p / V_b$

$= 1 - V_p / V_b$

$= 1 – m/l_p / m/ l_b$

$= 1 - l_b / l_p$

Therefore % Porosity = $(1 - l_b / l_p) \times 100$

Compressibility of a tablet also depends on bulk density of granules.

% Compressibility = $P_b – P_u / P_b \times 100$

Where P_u = Bulk density at untapped condition or loose bulk density or untapped bulk density.

Bulk density depends on granule size as granule size decreases, bulk density decreases.

4. Flow properties: For the movement of granules from hopper to die cavity sufficient flow properties are essential. Improper flow cause weight variation of content uniformity. Factors affecting flow properties are:

a) Frictional forces
b) Surface tension forces
c) Mechanical forces caused by interlocking of particles of irregular shape
d) Electrostatic forces
e) Cohesive or Van der Waals forces.
f) Flow properties of granules can be measure by two methods:

(a) Angle of repose: It is maximum angle between the surface of a pile of powder and horizontal plane, when powders are allowed to flow freely from a certain height. It can be measured by fixed funnel and cone method. Powder or granulation is allowed to flow through the funnel until the apex of conical pile just touches the tip of the funnel. Measuring the radius (r) and height (h) of pile repose angle can be measured.

Angle of Repose$\leq 30 \rightarrow$ Free flowing material
Angle of Repose $\geq 40 \rightarrow$ Poorly flowing material

(b) Hopper Flow rate: Granules are allowed to flow from the conical hopper onto a recording balance device and dw/dt is calculated [27, 28, 29].

Evaluation of Buffered Tablet:

1. General Appearance: The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odor, taste etc.

2. Size and Shape: It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micrometer or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value. In case of buffered tablet, the size of tablet is always large because of high quantity of buffering agent is / are required for the *in situ* buffering.

3. Hardness and Friability: Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shakes of handling in manufacture, packaging and shipping. Hardness generally measures the tablet crushing strength. The hardness should be such that it can immediately break inside the body so that it can immediately produce buffering. By friability it can be interpreted that the hardness is acceptable.

4. Disintegration Test (U.S.P.): The U.S.P. device to test disintegration uses 6 glass tubes that are 3" long; open at the top and 10 mesh screen at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2°C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. Move the basket containing the tablets up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. The buffered tablet should have immediate disintegration [30].

Evaluation of Buffered capsules: Whether capsules are produced on a small scale or large scale all of them are required to pass not only the disintegration test, weight variation test and percentage of medicament test but a visual inspection must be made as they roll off the capsule machine onto a conveyor belt regarding uniformity in shape, size, color and filling. As the capsules moves in front of the inspectors the visibly defective or suspected of being less than the perfect are picked out.

The hard and soft gelatin capsules should be subjected to following tests for their standardization.

1. Shape and size
2. Color
3. Thickness of capsule shell

4. Leaking test for semi-solid and liquid ingredients from soft capsules
5. Disintegration tests
6. Weight variation test
7. Percentage of medicament test

In official books the following quality control tests are recommended for capsules:

1. Disintegration test: For performing disintegration test on capsules the tablet disintegration test apparatus is used but the guiding disc may not be used except that the capsules float on top of the water. One capsule is placed in each tube which are then suspended in the beakers to move up and down for 30 minutes, unless otherwise stated in the monograph. The capsules pass the test if no residue of drug or other than fragments of shell remains on No. 10 mesh screen of the tubes.

2. Weight variation test: 20 capsules are taken at random and weighed. Their average weight is calculated, then each capsule is weighed individually and their weight noted. The capsule passes the test if the weight of individual capsule falls within 90-110% of the average weight. If this requirement is not met, then the weight of the contents for each individual capsule is determined and compared with the average weight of the contents. The contents from the shells can be removed just by emptying or with the help of small brush. From soft gelatin capsules the contents are removed by squeezing the shells which has been carefully cut. The remainder contents are removed by washing with a suitable solvent. After drying the shells, they are weighed and the content weights of the individual capsules are calculated. The requirements are met if (1) not more than 2 of the differences are greater than 10 % of the average net content and (2) in no case the difference is greater than 25 %.

3. Capsule stability: Unprotected soft capsules (i.e., capsules that can breathe) rapidly reach equilibrium with the atmospheric conditions under which they are stored. This inherent characteristic warrants a brief discussion of the effects of temperature and humidity on these products, and points to the necessity of proper storage and packaging conditions and to the necessity of choosing an appropriate retail package. The variety of materials capsulated, which may have an effect on the gelatin shell, together with the many gelatin formulations that can be used, makes it imperative that physical standards are established for each product.

General statements relative to the effects of temperature and humidity on soft gelatin capsules must be confined to a control capsule that contains mineral oil, with a gelatin shell having a dry glycerin to dry gelatin ratio of about 0.5 to 1 and a water to dry gelatin ratio of 1 to 1, and that is dried to equilibrium with 20 to 30 % RH at 21 to 24°C, the physical stability of soft gelatin capsules is associated primarily with the pick-up or loss of water by the capsule shell. If these are prevented by proper packaging, the above control capsule should have satisfactory physical stability at temperature ranging from just above freezing to as high as 60°, for the unprotected control capsule, low humidities (less than 20 % RH), low temperature (less than 2°C) and high temperatures (greater than 38°C) or combinations of these conditions have only transient effects. The capsule returns to normal when returned to optimum storage conditions. As the humidity is increased, within a reasonable temperature range, the shell of the unprotected control capsule should pick up moisture in proportion to its glycerin and gelatin content [31].

Evaluation of Buffered Microspheres:

1. Particle size analyser: Microsphere (50 mg) was suspended in distilled water (5mL) containing 2%w/v of tween 80, to prevent microsphere aggregation, the above suspension is sonicated in water bath and the particle size was expressed as volume mean diameter in micrometer.

2. Optical microscopy: This method was used to determine particle size by using optical microscope (Meizer OPTIK) The measurement was done under 450x (10x eye piece and 45x objective) and100 particles were calculated.

3. Scanning electron microscopy (SEM): Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample slub with the help of double sided sticking tape and coated with goldfilm under reduced pressure.

4. Swelling index: This technique was used for Characterization of sodium alginate microspheres were performed with swelling index technique Different solution (100mL) were taken such as (distilled water, buffer solution of pH(1.2, 4.5, 7.4) were taken and alginate microspheres (100mg) were placed in a wire basket and kept on the above solution and swelling was allowed at 37 ^{o}C and changes in weight variation between initial weight of microspheres and weight due to swelling was measured by taking weight periodically and soaking with filter paper.

5. Thermal analysis: Thermal analysis of microcapsule and its component can be done by using-

Differential scanning calorimetry (DSC)
Thermo gravimetric analysis (TGA)
Differential thermometric analysis (DTA)

Accurately the sample was weighed and heated on alumina pan at constant rate of 10oc/min under nitrogen flow of 40 ml/min.1 UV-FTTR (Fourier transform infrared) The buffer polymer interaction and also degradation of drug while processing for microencapsulation can be determined by FTIR.24

6. Stability studies: By placing the microspheres in screw capped glass container and stored them at following conditions:

1. Ambient humid condition
2. Room temperature (27+/-2 ^{0}C)
3. Oven temperature (40+/-2 ^{0}C)
4. Refrigerator (5 ^{0}C -8^{0}C).

It was carried out of a 60 days and the buffer content of the microsphere was analysed.

7. Zeta potential: The polyelectrolyte shell was prepared by incorporating chitosan of different molecular weight into the W_2 phase and the resulting particles were determined by zeta potential measurement [32].

CONCLUSION: It has been observed that *in situ* buffered formulation is an effective approach for acid labile drugs. There are many formulations which could enhance the acid stability of the drugs but buffered formulation approach is the most effective and low cost approach. So in future in situ buffered approach will play an important role in the advancement of medicinal field specially in case of instability of the drug due to internal environment of the body.

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